SAFETY OF PESTICIDES USED TO CONTROL ADULT MOSQUITOES
(Pyrethrins, Pyrethroids, and Piperonyl Butoxide)

Questions and Answers for Public Health Professionals

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1. What is the primary method used to control West Nile virus?

Mosquito control is the most effective means of reducing the risk of people becoming infected with West Nile virus (WNV). Mosquito control targets both the aquatic, immature stages of the mosquito and the adult stage (CDHS, 2005a).

Larval control Control of larval mosquitoes is the backbone of most mosquito control programs in California. Pesticides added to the water to kill mosquito larvae are called larvicides. These products may be applied by hand, with a power backpack, from all terrain vehicles (ATV's) or trucks, and in very large or inaccessible areas with helicopters and airplanes. Pesticides used for larviciding include, bacterial products (*Bacillus thuringiensis* var. *israelensis* (Bti) and *B.sphaericus* (Bs)); surface agents (highly refined mineral oils or monomolecular films that spread across the surface of the water); and insect growth regulators methoprene and dimilin (chemicals that are added to the water to disrupt the normal maturation process of mosquito larvae). For more information on larvicidal agents, please refer to the fact sheet titled "Pesticides and Mosquito Control" (US EPA, 2002).

Adult mosquito control Adult mosquito control is a means to rapidly knockdown biting adult mosquitoes. This can become necessary when larval control measures are insufficient or not feasible. Adulticiding may be initiated when there is evidence of significant WNV transmission in a region. The most common method of adult mosquito control (adulticiding) is ultra-low volume (ULV) spraying. ULV spraying (also occasionally called cold fogging) is the process of putting very small amounts of liquid (typically 4 ounces per acre or less) into the air as a fine mist of droplets. These droplets float on the air currents and quickly kill mosquitoes that come into contact with them. ULV adulticides are applied when mosquitoes are most active – typically early evening or pre-dawn.

ULV spraying is usually done over geographic areas consisting of several acres to many square miles. Unlike agricultural or structural pesticide applications where the chemical is applied directly to a crop or structure, a ULV formulation is sprayed into the air column where it can contact and kill active mosquitoes. Aerial movement of the ULV product is an essential part of the application. ULV applications are only done during environmental conditions that ensure desirable product movement.

2. What pesticides are used to control mosquitoes that carry West Nile virus?

In California, two classes of pesticides, each combined with a synergist chemical, are commonly used for adult mosquito control.

Pyrethrins are the active ingredients in pyrethrum, an extract of the African flower *Chrysanthemum cineriaefolium*. Pyrethrins are natural insecticides that act by blocking chemical signals at nerve junctions.

Pyrethroids are synthetic pesticides that are very similar to pyrethrins in their chemical structure and mode of action. Permethrin, resmethrin, deltamethrin, and sumithrin (also known as D-phenothrin) are pyrethroid insecticides that may be used for adulticiding. Pyrethroids are more light-stable and have a longer duration of activity against insects than pyrethrins.

Piperonyl butoxide (PBO) is a synergist that is usually incorporated with pyrethrins and pyrethroids. PBO enhances the effect of these insecticides by inhibiting cytochrome P450, a class of enzymes that break the down the pesticides. This allows the insecticides to be effective with less active ingredient than would otherwise be required.

In addition, as with all pesticide formulations, the pesticides used for adulticiding contain inactive ingredients, typically petroleum distillates.

Pyrethrins, pyrethroids, and PBO are widely used for home, garden, agricultural and structural (building) pesticide applications. They are also found in products to control head lice or the fleas on pet animals.

3. How do these pesticides work?

Both pyrethrins and pyrethroids act on the nervous system of insects by inactivating sodium channels in the insect nervous system. Because mammals rapidly detoxify these compounds, humans are less susceptible to systemic effects by this mode of action.

4. Who approves the use of these pesticides?

US EPA approves the use of pesticides nationally and the California Department of Pesticide Regulation (CDPR) approves their use in California. Before pesticides are registered by US EPA or CDPR, they must undergo laboratory testing for acute and chronic health effects. In these tests, laboratory animals are purposely fed a pesticide at high doses (usually the pure or technical material) for an extended period of time specifically to see if toxic effects occur. These tests help scientists judge how these chemicals might affect humans, domestic animals, and wildlife in the case of exposure.

The US EPA has guidelines that require testing of pesticides for their potential to cause cancer. These studies involve feeding laboratory animals large daily doses of the pesticide over most of the lifetime of the animals. Based on these tests, as well as any other available information, EPA gives the pesticide a rating for its potential to cause cancer in humans.

5. What are the potential health effects of pyrethrins and pyrethroids?

Acute

Pyrethrins

In acute oral dosing studies with pyrethrins, rats exhibited difficulty breathing, lack of coordination, sprawling of limbs, tremors, aggression, sensitivity to external stimuli, twitching and exhaustion (Litchfield, 1985).

In humans, dermatitis is the most common health effect reported following direct contact with pyrethrins. Descriptions range from local erythema to vesicular eruptions (Ecobichon, 1990). These dermal effects may be due to allergenic or irritant effects of pyrethrins, or to irritation caused by PBO or by petroleum distillates used in the formulation process (O'Malley, 2001).

Allergic rhinitis, conjunctivitis, and asthma have been reported following human exposure to pyrethrins. Rare but potentially severe reactions following direct dermal or respiratory exposure to pyrethrins include hypersensitivity pneumonitis, nonfatal and fatal anaphylactic reactions (Carlson, 1977; CDC, 2000; Wagner, 1994; Wagner, 2000; Wax, 1994).

The chief allergen in unpurified pyrethrins is a lactone compound, pyrethrosin (Penagos et al., 2001). Current pyrethrin formulations are purified and theoretically do not contain the lactone sensitizer. Sensitization reactions to purified pyrethrin products have not been well documented in the recent literature (Penagos et al., 2001).

Pyrethroids

Although allergic contact dermatitis and asthma due to pyrethroids have been alleged, they have not been well documented (Kolmodin-Hedman, 1982; Wagner, 1994; Penagos et al., 2001). Unique skin paresthesias, manifested by numbness, itching, burning, tingling, and warmth, and often described as a sensation of insects crawling on the skin, have been described following exposure to certain pyrethroids. The paresthesias are due to the effects on sodium channels of the nerve terminals in skin (Penagos et al., 2001).

Based on occupational studies, mild acute exposure may result in dizziness, headache, nausea, anorexia and fatigue. At high doses, such as when workers have been soaked with concentrated pyrethroids, or after intentional ingestion, the following symptoms have been reported: muscular fasciculations, convulsions, pulmonary edema, and coma (He et al., 1989)
Piperonyl Butoxide PBO causes skin irritation in laboratory animals, but no skin irritation was observed in human studies (NPTN, 2000; Penagos et al., 2001). No other acute health effects due to PBO alone have been reported. This may be partly due to the fact that it is not used alone but in conjunction with other pesticides.

Petroleum Distillates The term "petroleum distillate" encompasses a wide variety of petroleum-based compounds. In general, this class of compounds may produce eye, skin, and respiratory irritation, and symptoms of CNS depression, such as headache, dizziness, nausea, and vomiting. Since the components of petroleum compounds are "volatile", they will "evaporate" from any solid surface within hours.

Chronic

Pyrethrins The data on reproductive toxicity of pyrethrins in animals varies by species. Rabbits fed moderate doses (up to 90 mg/kg) of pyrethrins during a sensitive period of pregnancy had normal litters. There were no birth defects in rabbit litters exposed to pyrethrins. Rats fed very high doses (5,000 mg/kg) of pyrethrins for three weeks before their first mating produced a low birth weight litter (CDPR, 2005). As is typical for many chemicals, human data on reproductive toxicity on pyrethrins are lacking.

US EPA classified pyrethins as "likely to be carcinogenic to humans by the oral route" in 1999 (US EPA, 1999). This evaluation was based on results from standard two-year carcinogenicity studies where rats and mice were exposed to high-dose pyrethrins in their diet. In those studies, the incidence of thyroid tumors was greater in male and female rats exposed to pyrethrins than in untreated control rats. In addition, pyrethrin-treated female rats developed benign liver tumors. US EPA re-evaluated pyrethrins in 2004 and classified pyrethrins in the group: "Suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential" (US EPA, 2004). This category is described as one "which raises a concern for carcinogenic effects but is judged not sufficient for a conclusion as to human carcinogenic potential." Researchers found that farmers exposed to pyrethrins used for pest control on livestock had an increased risk of developing leukemia (Brown et al., 1990). Because farmers are exposed to multiple chemicals, these results require further study to evaluate the specific effects of pyrethrins.

Pyrethroids Rats fed high doses of resmethrin had litters with decreased viability and body weight gain at the high dose in rats; rabbits fed high doses of resmethrin showed an increase in abortions and fetal resorptions (CDPR, 2005). In one animal study, permethrin impeded fertility but was not teratogenic. Permethrin and resmethrin are not mutagenic.

Specific pyrethroids have been evaluated for their potential to cause cancer. Permethrin has been classified by US EPA in the category "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." Other pyrethroids are classified as possible human carcinogens (Group C) where US EPA concluded that there was limited evidence of carcinogenicity in animals. This category is similar to the "suggestive evidence of carcinogenicity" category. Pyrethroids classified as Group C include bifenthrin, tetramethrin and cypermethrin. These pyrethroids, which are not commonly used for WNV mosquito control, increased incidences of urinary bladder and liver tumors in mice (bifenthrin), testicular interstitial cell tumors in male rats (tetramethrin), and lung tumors in female mice (cypermethrin). Not all pyrethroid insecticides have been evaluated for cancer risk. For two pyrethroids commonly used for WNV adulticiding (sumithrin and resmethrin), no US EPA evaluation is available.

Some pyrethroids have tested positive in cytogenetic studies. For example, some pyrethroids (permethrin, cypermethrin, deltamethrin, and fenvalerate) increased chromosome damage (chromosomal aberrations) in bone marrow cells of mice after treatment with the insecticide (ATSDR, 2003). There is some evidence that chromosomal aberrations may predict cancer risk.

Pyrethroids may affect endocrine hormone function at high doses. Permethrin was

associated with gynecomastia (excessive development of the male mammary glands) in male Haitian refugees treated with the insecticide in the early 1980's (Brody, 2003). Since then, high dose *in vitro* studies have shown the anti-androgenic activity of several pyrethroids (Eil, 1990). Some pyrethroids have been found to be estrogenic in *in vitro* studies (Kim et al., 2004; Go et al., 1999; Garey, 1998). However, adverse endocrine disruption effects (anti-androgenic or estrogenic effects) were not observed when esfenvalerate, fenvalerate, or permethrin were administered at lower doses to rats (Kunimatsu et al., 2002). The clinical implications of these findings are unclear and they need to be further investigated in terms of potential effects of pyrethroids on the development of both cancer and reproductive toxicity in humans.

Piperonyl Butoxide
PBO is not a developmental or reproductive toxicant in animals.

Two published studies have shown that PBO administered long-term in the diet to male female rats and mice produced treatment related increases in liver cancer (Takahashi et al., 1994; Takahashi et al., 1997). However, several other studies in rats did not find evidence of carcinogenic potential (NTP, 1979; Maekawa et al., 1985; Butler et al., 1998). A more recent EPA (1995) review rates PBO as a "Group C (Possible Human Carcinogen"), although this classification pre-dates several of the available studies. As stated above, EPA defines Group C such chemicals as agents with limited evidence of carcinogenicity in animals in the absence of human data.

6. How safe are these pesticides?

No pesticide is completely safe. All individuals should take steps to minimize exposure to any pesticide.

While the pesticides used for mosquito control can cause adverse health effects under certain circumstances, described above, the available data suggest that they are relatively safe when applied by ULV spraying according to label instructions for the following reasons.

Pesticides are unstable Pyrethrins are extremely photosensitive and break down within hours in the presence of sunlight and air. Evening applications are likely to degrade by the morning, and much of the product does not reach the ground (Moore, 1993; Knepper, 1996). While pyrethroids are more stable, this varies with the compound. Permethrin has a half-life of about five days in sunlight and resmethrin is more stable, with a half life of about 30 days (Beasley, 2000). The half-life of PBO is about four days in soil and up to two days in water (NPTN, 2000).

Very low dosage rates of pesticides are used Typically less than one ounce per acre is applied either by ground or air. An application rate of 0.66 ounces of product per acre (0.0025 pounds per acre), which is typical for pyrethrin products, equate to 0.000015 ounce per square foot, assuming that all of the pesticide reaches the ground.

Pesticides are poorly absorbed through the skin Pyrethrins, pyrethroids, and piperonyl butoxide are all poorly absorbed through the skin (Franz, 1996; Wester et al., 1994). When applied directly to the scalp of human volunteers, as in shampoo applications, absorption is greater (approximately 8%) than when applied to the forearm (approximately 2%), (Wester et al., 1994).

No evidence of exposure following ULV spraying The only study to quantitate human exposure to pesticides following spraying for WNV found that there was no increase in urine metabolite concentrations of the metabolites of naled (an organophosphate), permethrin, or d-phenothrin after ULV spraying compared with baseline (CDC, 2005). Use of sensitive analytic methods in these studies indicated that the urine pesticide metabolite concentrations measured were low (parts per billion). The concentration of urine metabolites were comparable with those measured in the general population (CDC, 2003b; Heudorf, 2001). In certain participants, investigators found an association between home and/or work application of pesticides and pesticide metabolite concentrations.

The Centers for Disease Control and Prevention (CDC) has detected several permethrin metabolites in urine samples across a broad spectrum of the US population, suggesting that in spite of relatively low environmental stability and poor skin absorption, human exposures occur commonly (CDC, 2005). CDC did not evaluate the reason for permethrin applications or whether applications and exposures occurred indoors or outdoors. Indoor pyrethrin and pyrethroid applications are more persistent, and therefore indoor exposure levels may be higher than those that occur outdoors.

Population health effects following spraying From 1999-2002, nine states reported 37 cases of pesticide illness related to pyrethroids used for WNV control, although the types of illnesses were not specified. Pyrethroids, primarily sumithrin, accounted for about 28% of all reported cases (CDC, 2003a). In New York City, ULV spraying with pyrethroids was not associated with population-level increases in rates of emergency-room visits for asthma in 1999-2000 (Karpati et al., 2004).

Population-level health effect data following pyrethrin applications are not available.

7. What are the health risks of ULV spraying for WNV control? Who is at risk?

There is a small risk that people who have already been sensitized (are allergic) to pyrethrins may have an allergic reaction, such as allergic contact dermatitis or exacerbation of asthma, if they are re-exposed.

There is a small chance that people who are chemically sensitive may experience a worsening of their chemically-related conditions if they are re-exposed.

There is a small chance that people with preexisting asthma or chronic respiratory conditions may experience a worsening in these conditions if they are exposed.

Individuals in higher risk categories like those listed above should contact their local mosquito control agency for additional information about local mosquito control activities.

All individuals, especially pregnant women, should take simple precautions to avoid exposure to pesticides, including those used in mosquito control.

Workers, especially mixers, loaders, and applicators of pesticide formulations, are at greater risk for exposure to pesticides than the general public. Workers who are exposed to these pesticides as a result of their regular tasks may experience health effects such as nausea and skin, eye, and upper respiratory irritation (Gupta et al., 1980). In order to

minimize occupational exposure, employers should ensure that all precautions specified on the pesticide label are followed.

8. How likely is it that the public will be exposed to pesticides used for WNV spraying?

ULV technology, which uses very low doses of pesticides, and the practice of spraying between dusk and dawn, when most people are indoors, help to minimize exposure to these pesticides. Since the pesticides used are unstable in sunlight and air, they are rapidly degraded and it is unlikely that exposure will occur the day following spraying. Exposure to pesticides may occur if people are outdoors in an area while spraying is occurring.

9. Do the health risks justify ULV spraying with pesticides for WNV mosquito control?

Although 80% of human WNV infections are mild and often clinically unapparent, illnesses are potentially serious. The most common form of illness is WNV fever. The clinical course of WNV fever ranges from a mild febrile illness of several days' duration to debilitating fatigue, aching, and weakness that may last for weeks or months (Hayes et al., 2005). Approximately 1 in 150 infections results in severe neurological disease with potential permanent sequelae. The spectrum of neurological disease includes meningitis, encephalitis, and paralysis. Of these, encephalitis shows a marked predilection for the elderly, while meningitis tends to be more prevalent in the young. In 2004, CDC reported 100 deaths out of 2539 cases in the US (3.9% case fatality rate) (CDC, 2004).

Studies evaluating the effectiveness of WNV control have shown that ULV spraying for mosquitoes in areas with high rates of human disease results in a decrease in the rates of human infection immediately following ULV applications (DeFeyter, 2004; Nasci, 2004).

A public health analysis conducted by New York City Department of Health determined that no significant adverse public health impacts would be expected from exposure to the adulticides when applied for the purposes of mosquito control and that any effects would likely be less than those of WNV (NYCDOH, 2001).

10. How can pesticide exposure be minimized?

Although mosquito control pesticides and the techniques used pose low risks, exposure to pesticides should be minimized. Some common sense steps to help reduce possible exposure to pesticides include:

Pay attention to the local media for announcements about spraying and remain indoors during applications in the immediate area.

People who suffer from chemical sensitivities or feel spraying may aggravate a preexisting health condition, may consult their physician or local health department and take special measures to avoid exposure.

Close windows and turn off window-unit air conditioners when spraying is taking place in the immediate area.

Do not let children play near or behind truck-mounted applicators when they are in use.

11. Who should be contacted if illness is suspected due to exposure to ULV spraying?

Those who feel they have experienced illness due to pesticides used for ULV mosquito control should:

Call the Poison Control Center for immediate advice: (800) 222-1222.

Consult their health care providers. Physicians are required to report all suspected pesticide illness to the local health officer. Health officers are required to file a pesticide illness report for all reported suspected pesticide illnesses, including occupational pesticide illnesses (OEHHA 2005; CDHS, 2005b). Health care providers are now required to report pesticide illnesses to the local health officer using the Confidential Morbidity Report (CDHS, 2005c). State programs use these reports to conduct illness surveillance for a variety of conditions.

Those with concerns about their pets should consult their veterinarian.

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